SERUM KERATAN SULFATE LEVEL FOLLOWING CHEMONUCLEOLYSIS

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Serum Keratan Sulphate Level Following Chemonucleolysis

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In chemonucleolysis, accuracy of injection can be in doubt if the patient fails to respond. Discography preceding chemonucleolysis is associated with increased neurologic complications. Biplane fluoroscopy may fail to provide a clear picture on many occasions. The serum keratan sulphate levels were estimated in patients undergoing chemonucleolysis to ascertain if this could be used as a biochemical indicator to confirm accurate needle placement and to predict outcome. Serum keratan sulphate levels rose significantly following chemonucleolysis during the first 3 days ($P < 0.01$). The rise was not significantly different, however, in patients who had improvement in their leg pain from those who did not improve ($P = 0.35$). Serum keratan sulphate level estimation before chemonucleolysis and at 24 or 48 hours following the procedure can be used to confirm accuracy of needle placement, but the rise in keratan sulphate is not predictive of the clinical outcome of the procedure. [Key words: chemonucleolysis, keratan sulphate]

CHEMONUCLEOLYSIS HAS BEEN USED in the treatment of symptomatic lumbar disc herniation for the past 27 years. Double-blind studies have established its place in the treatment of sciatica.[5] Of patients with sciatica due to lumbar disc herniation, however, 20–30% fail to respond to this procedure,[6] and some of the discs excised from patients who had failure of chemonucleolysis do not show evidence of any effect of the enzyme chymopapain.[12] Inaccurate needle placement has been suggested as a reason for some of the failures.[4]

During chemonucleolysis, a needle is passed into the disc under two-plane fluoroscopic control, but there are occasions when the operator is unsure about the accuracy of needle placement. This is particularly true when there is either too much or too little resistance to the injection. If these patients fail to improve symptomatically following the procedure, then doubts about the accuracy of needle placement increase. Failure to obtain significantly better results in one of the placebo-controlled trials of chemonucleolysis[8] has been attributed by critics to inexperience of the surgeons who injected the enzyme.[4]

Discography preceding the injection of the enzyme confirms accurate needle placement. However, an increased incidence of neurologic complications when discography preceded the procedure has been reported.[3] Some fear that the effect of the enzyme may be decreased by inactivation or dilution of the enzyme by the injected contrast material.[2] The drug is supplied with the advice that discography should not be done before chymopapain injection.[3]

Presently, no other reliable method is available to confirm the accuracy of needle placement during chemonucleolysis. We looked for a postoperative test to confirm accuracy of needle placement so that failure of chemonucleolysis due to inaccurate placement of injection could be excluded. Detection of products of discolysis in urine and blood is indirect proof of accurate needle placement. In the urine, increased excretion of glycosaminoglycans, such as chondroitin sulphate and keratan sulphate, occurs following chemonucleolysis.[9] Most glycosaminoglycans are found in noncartilaginous tissues in significant amounts, whereas keratan sulphate is practically specific for the cartilaginous tissues including intervertebral disc.[10] It has been shown that a significant rise in serum keratan sulphate levels occurs following chemonucleolysis in animals and humans.[1,7] However, the validity of keratan sulphate level as a criterion for postoperative confirmation of accurate needle placement in chemonucleolysis has not been examined before. Moreover, if keratan sulphate levels are indicative of effective lysis of the nucleus pulposus, it could be predictive of the clinical outcome following chemonucleolysis.

In this prospective study, we examined the serum keratan sulphate level following chemonucleolysis to ascertain if it could be used to confirm the accuracy of needle placement and to predict the subsequent outcome of the procedure.

PATIENTS AND METHODS

Twenty patients undergoing chymopapain chemonucleolysis for symptomatic lumbar disc herniation were studied prospectively. The study included 11 women and 9 men aged 20–47 years (mean, 37 years). Seven patients had disc herniation at L4–L5 and 13 at L5–S1.

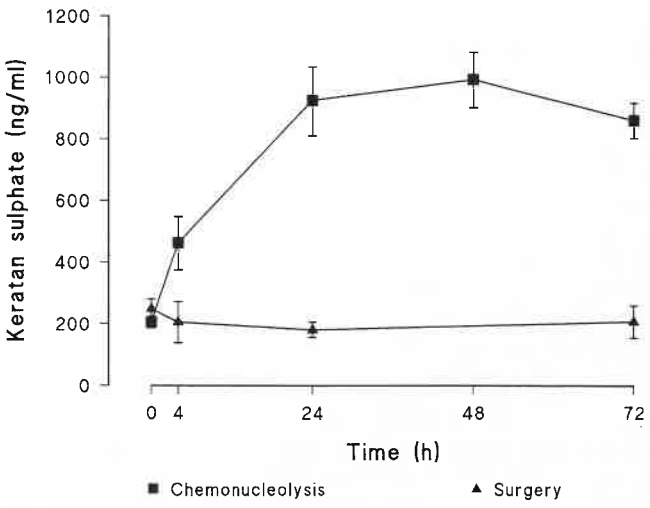

Fig 1. Serum keratan sulphate levels in patients receiving chemonucleolysis treatment (N = 20) and those receiving disc surgery (N = 10). Samples were taken up to 72 hours after the procedure. Results are given as mean ± SEM.

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Table 1A. Keratan Sulphate Level in Relation to Leg Pain: Significant Clinical Improvement

Patient No.	Level L4-5/ L5-S1	Leg Pain		Keratan Sulphate (ng/ml)		
		Pre-injection	3 mo Post-injection	Pre-injection	24 hr	72 hr
1	5-1	100	0	251	800	656
2	4-5	80	0	270	1088	816
3	4-5	25	0	320	1200	976
4	4-5	90	0	218	212	633
5	4-5	55	10	180	624	992
6	5-1	100	5	98	320	531
7	4-5	90	5	444	584	1060
8	5-1	50	5	160	1088	976
9	5-1	50	0	174	883	800
10	5-1	70	0	272	1766	1184
11	5-1	70	0	120	880	760
12	4-5	45	0	192	488	980
13	4-5	100	10	236	2272	1520
14	5-1	30	0	176	787	902
15	5-1	70	25	199	960	1056
16	5-1	60	0	118	1280	800
Mean:				214	952	915
SEM:				22	130	60

Table 1B. Keratan Sulphate Level in Relation to Leg Pain: No Significant Improvement

Patient No.	Level L4-5/ L5-S1	Leg Pain		Keratan Sulphate (ng/ml)		
		Pre-injection	3 mo Post-injection	Pre-injection	24 hr	72 hr
17	5-1	90	90	90	1344	834
18	5-1	75	75	164	778	637
19	4-5	50	100	161	327	370
20	5-1	65	50	246	900	774
Mean:				165	837	654
SEM:				32	209	103

The diagnostic criteria included 1) the presence of root pain in the sciatic distribution extending below the level of knee; 2) root irritation signs (limitation of straight leg raising, positive bowstring test, cross leg pain, etc.) and/or root compression signs (weakness of extensor/flexor of hallux, paraesthesia at L5 or S1 distribution, loss of ankle jerk, etc.); and 3) a positive myelogram.

Ten patients undergoing disc excision were studied as a control group. This group comprised six men and four women aged 20–55 years (mean, 35 years). Five had L4–5 disc herniation, and five had L5–S1 disc herniation. Diagnostic criteria were the same as that for the injection group.

Each patient undergoing chemonucleolysis received an injection of 4,000 picoKatals of Discase (Travenol Laboratories, Thetford, Norfolk, England) into a single disc under two-plane fluoroscopic control. All patients were allowed to mobilize as soon as there was satisfactory relief of pain. The preoperative and postoperative care of these patients was standardized. All surgical patients had limited disc excision.

All patients were assessed by independent examiners unaware of the method of treatment assigned to the patients. Subjective measurements included disability score, back pain, and leg pain measurements on visual analogue scales (100-mm scale) and anxiety and depression scores. Objective measurement consisted of the physical impairment score.[11] All patients were reassessed 6–12 weeks after the treatment.

Keratan Sulphate Assay. Blood samples were collected before the procedure and at 24 and 72 hours after the injection or operation. Eight patients also had blood samples taken at 4 hours and 13 patients at 48 hours. The serum was separated within 1 hour and stored at −20 C until the amount of keratan sulphate was estimated.

Table 2. Variations in Keratan Sulphate Levels with Age and Sex

	Keratan Sulphate Levels (ng/ml) (mean ± SEM)		
	Preinjection	24 hr	72 hr
Age (yr)			
20-30	180 ± 32	813 ± 304	826 ± 118
31-40	203 ± 36	949 ± 86	801 ± 74
41-50	218 ± 30	977 ± 167	912 ± 92
Sex			
Female	191 ± 21	956 ± 127	818 ± 79
Male	233 ± 32	884 ± 199	908 ± 91

Serum keratan sulphate was estimated by enzyme-linked immunosorbent assay (ELISA) using specific monoclonal antibodies against keratan sulphate. The method of assay used has been described previously.[10]

Statistical Methods. The groups were compared according to parametric and nonparametric methods as appropriate (the Mann–Whitney U test, the Spearman correlation coefficient, and the Student *t* test).

RESULTS

Keratan sulphate levels for the disc surgery group and the chemonucleolysis group before the procedure were not significantly different (Figure 1). Following disc surgery, there were no significant increases in the serum keratan sulphate level, but all patients who had chemonucleolysis showed a dramatic increase during the first 3 days. Keratan sulphate levels were significantly raised as early as 4 hours following the injection (Figure 1). The level continued to rise at 24 and 48 hours. The levels at 72 hours after injection were still significantly higher compared with the preinjection levels. In the majority of patients, the peak level of keratan sulphate in serum appeared to be at 48 hours after injection. The rise in serum keratan sulphate level after chemonucleolysis varied from 130% to 1400%, whereas the maximum rise in the surgical group was 45%.

It was possible to group the patients into those who showed significant improvement and those who did not, based on the improvement in leg pain. The assessment scores of leg pain are shown in Table 1. Sixteen of 20 patients had significant reduction in leg pain. There were no significant differences in the rise in keratan sulphate at 24 and 72 hours between those who showed significant improvement in leg pain and those who did not ($P = 0.35$ at 24 hours; $P = 0.37$ at 72 hours) (Table 1).

Keratan sulphate results for the various age groups are shown in Table 2. In effect, there were no differences among the age groups. Similarly, there were no differences between the results for male and female patients (Table 2). The increase in keratan sulphate levels was significantly higher in the L5–S1 disc injection group than in the L4–5 group during the first 48 hours ($P = 0.08$ before surgery; $P = 0.03$ at 24 hours; $P = 0.04$ at 48 hours; and $P = 0.3$ at 72 hours). There was a negative correlation between the duration of sciatica and the rise in keratan sulphate at 24 hours ($P = 0.01$; N = 20) but this difference disappeared at 72 hours ($P = 0.29$; N = 20).

The assessment scores in the two groups are shown in Table 3. This demonstrates that there were reductions in the disability index score and psychological score in keeping with reduction in leg pain in those who improved after chymopapain injection.

DISCUSSION

Serum keratan sulphate levels in healthy persons do not vary significantly during the course of a single day or from day to day during

Table 3. Chemonucleolysis Assessment Scores

	Improved (n = 16)		*Not Improved (n = 4)*	
Age (mean)	35 yr		41 yr	
Sex	8 male/8 female		1 male/3 female	
Pain duration (mean)	22 weeks		25 weeks	
Level injected	6 L4-5; 10 L5-S1		1 L4-5; 3 L5-S1	
	Preinjection	*Postinjection*	*Preinjection*	*Postinjection*
Leg pain (100-mm scale)	67	3.7	70	78
Back pain (100-mm scale)	17	13	38	63
Disability index (9-point scale)	6.2	2.3	5.3	5.3
Physical Impairment score (normal = 0)	18	10	25	17
Psychological score (ideal = 0)	22	18	26	32

Results are given as mean values for each parameter.

the course of a week.[1] Therefore, a single keratan sulphate level estimation is representative of a person's keratan sulphate concentration in serum during normal metabolic activities. A significant variation in the keratan sulphate concentration after surgery or chemonucleolysis is likely to be due to the effect of the procedure.

The significant rise in keratan sulphate at 4 hours postinjection suggests that chymopapain is rapidly effective in the breakdown of proteoglycans of the disc. The keratan sulphate levels were steady between 24 and 48 hours and then started to decline. In contrast, patients who underwent disc surgery had no increase in serum keratan sulphate levels.

The lack of a significant difference in keratan sulphate levels among different age groups suggests that the chemical composition of the nucleus pulposus may not be affected by the aging process in the third to fifth decade. Similarly, sex had no effect on keratan sulphate levels. A significantly higher rise in keratan sulphate in the patients who had L5–S1 disc injection is surprising, given the fact that the L4–5 disc is larger than the L5–S1 disc. More rapid diffusion of the glycosaminoglycans out of the L5–S1 disc may be a possible explanation, because this difference disappeared at 72 hours.

This study confirms that the serum keratan sulphate level rises dramatically after chemonucleolysis. The rapid rise of keratan sulphate level after chemonucleolysis at 24, 48, and 72 hours suggests that estimation of keratan sulphate can be used as a postinjection test to confirm the accuracy of needle placement. The lack of a significant difference in the keratan sulphate levels between the 80% of patients who improved and the 20% who did not, would indicate that the level by which serum keratan sulphate rises after disc injection cannot be used to predict outcome with respect to symptoms.

CONCLUSIONS

The serum keratan sulphate level rises dramatically after chemonucleolysis. Estimation of keratan sulphate 24 or 48 hours postinjection can be used to confirm accurate placement of the injection. Serum keratan sulphate level is not predictive of the outcome of chemonucleolysis.

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